

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 September 2003 (25.09.2003)

PCT

(10) International Publication Number
WO 03/078421 A1

(51) International Patent Classification⁷: C07D 401/04,
409/14, 405/14, A61K 31/445, A61P 37/00, 11/06, 31/16

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(21) International Application Number: PCT/SE03/00442

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 17 March 2003 (17.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0200843-1 19 March 2002 (19.03.2002) SE

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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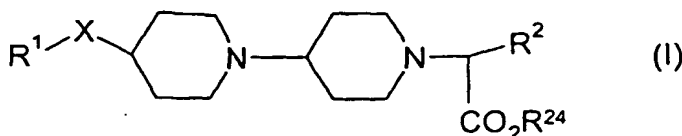
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Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PIPERIDINE DERIVATIVES USEFUL AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY



(57) Abstract: The present invention provides a compound of formula (I), wherein the variables are defined herein; to a process for preparing such a compound; and to the use of such a compound in the treatment of a chemokine (such as CCR3) or H1

mediated disease state.

PIPERIDINE DERIVATIVES USEFUL AS MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY

The present invention concerns piperidine derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in WO99/38514, WO99/04794 and WO00/35877.

Histamine is a basic amine, 2-(4-imidazolyl)-ethylamine, and is formed from histidine by histidine decarboxylase. It is found in most tissues of the body, but is present in high concentrations in the lung, skin and in the gastrointestinal tract. At the cellular level inflammatory cells such as mast cells and basophils store large amounts of histamine. It is recognised that the degranulation of mast cells and basophils and the subsequent release of histamine is a fundamental mechanism responsible for the clinical manifestation of an allergic process. Histamine produces its actions by an effect on specific histamine G-protein coupled receptors, which are of three main types, H1, H2 and H3. Histamine H1 antagonists comprise the largest class of medications used in the treatment of patients with allergic disorders, such as rhinitis and urticaria. H1 antagonists are useful in controlling the allergic response by for example blocking the action of histamine on post-capillary venule smooth muscle, resulting in decreased vascular permeability, exudation and oedema. The antagonists also produce blockade of the actions of histamine on the H1 receptors on c-type nociceptive nerve fibres, resulting in decreased itching and sneezing.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system.

Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

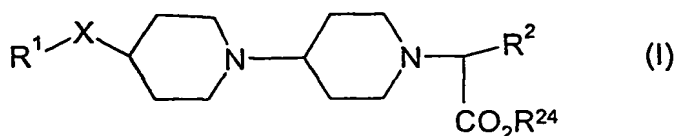
The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1 α and 1 β (MIP-1 α and MIP-1 β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

Viral infections are known to cause lung inflammation. It has been shown experimentally that the common cold increases mucosal output of eotaxin in the airways. Instillation of eotaxin into the nose can mimic some of the signs and symptoms of a common cold. (See, Greiff L *et al* Allergy (1999) 54(11) 1204-8 [Experimental common cold increase mucosal output of eotaxin in atopic individuals] and Kawaguchi M *et al* Int. Arch. Allergy Immunol. (2000) 122 S1 44 [Expression of eotaxin by normal airway epithelial cells after virus A infection].)

The present invention provides a compound of formula (I):



wherein:

X is CH₂, C(O), O, S, S(O), S(O)₂ or NR³;

R¹ is hydrogen, C₁₋₆ alkyl, aryl or heterocyclyl;

R² is C₃₋₇ cycloalkyl {optionally substituted by C₁₋₄ alkyl, aryl or oxo}, C₃₋₇ cycloalkenyl {optionally substituted by oxo, C₁₋₆ alkyl or aryl}, aryl or heterocyclyl;

wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by:

halogen, cyano, nitro, hydroxy, oxo, S(O)_pR⁴, OC(O)NR⁵R⁶, NR⁷R⁸, NR⁹C(O)R¹⁰, NR¹¹C(O)NR¹²R¹³, S(O)₂NR¹⁴R¹⁵, NR¹⁶S(O)₂R¹⁷, C(O)NR¹⁸R¹⁹, C(O)R²⁰, CO₂R²¹, NR²²CO₂R²³, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆

haloalkoxy, C₁₋₆ alkoxy(C₁₋₆)alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkylthio, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl (itself optionally substituted by C₁₋₄ alkyl or oxo), methylenedioxy, difluoromethylenedioxy, phenyl, phenyl(C₁₋₄)alkyl, phenoxy, phenylthio, phenyl(C₁₋₄)alkoxy, heterocyclyl, heterocyclyl(C₁₋₄)alkyl, heterocyclyloxy or heterocyclyl(C₁₋₄)alkoxy; wherein any of the immediately foregoing phenyl and heterocyclyl moieties are optionally substituted with halogen, hydroxy, nitro, S(O)_q(C₁₋₄ alkyl), S(O)₂NH₂, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)₂ (and these alkyl groups may join to form a ring as described for R⁵ and R⁶ below), CO₂H, CO₂(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl), NHS(O)₂(C₁₋₄ alkyl), C(O)(C₁₋₄ alkyl), CF₃ or OCF₃;

p and q are, independently, 0, 1 or 2;

R³, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁸, R¹⁹, R²⁰, R²¹ and R²² are, independently, hydrogen, C₁₋₆ alkyl (optionally substituted by halogen, hydroxy or C₃₋₁₀ cycloalkyl), CH₂(C₂₋₆ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)₂ (and these alkyl groups may join to form a ring as described for R⁵ and R⁶ below), S(O)₂(C₁₋₄ alkyl), S(O)₂NH₂, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)₂ (and these alkyl groups may join to form a ring as described for R⁵ and R⁶ below), CO₂H, CO₂(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl), NHS(O)₂(C₁₋₄ alkyl), C(O)(C₁₋₄ alkyl), CF₃ or OCF₃) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)₂ (and these alkyl groups may join to form a ring as described for R⁵ and R⁶ below), S(O)₂(C₁₋₄ alkyl), S(O)₂NH₂, S(O)₂NH(C₁₋₄ alkyl), S(O)₂N(C₁₋₄ alkyl)₂ (and these alkyl groups may join to form a ring as described for R⁵ and R⁶ below), cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)₂ (and these alkyl groups may join to form a ring as described for R⁵ and R⁶ below), CO₂H, CO₂(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl), NHS(O)₂(C₁₋₄ alkyl), C(O)(C₁₋₄ alkyl), CF₃ or OCF₃); alternatively NR⁵R⁶, NR⁷R⁸, NR¹²R¹³, NR¹⁴R¹⁵, NR¹⁸R¹⁹, may, independently, form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, 1,4-morpholine or 1,4-piperazine, the latter optionally substituted by C₁₋₄alkyl on the distal nitrogen;

R⁴, R¹⁷ and R²³ are, independently, C₁₋₆ alkyl (optionally substituted by halogen, hydroxy or C₃₋₁₀ cycloalkyl), CH₂(C₂₋₆ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)₂ (and these alkyl groups may join to form a ring as described for R⁵ and R⁶ above), S(O)₂(C₁₋₄ alkyl), S(O)₂NH₂, S(O)₂NH(C₁₋₄ alkyl), S(O)₂N(C₁₋₄ alkyl)₂ (and these alkyl groups may join to form a ring as described for R⁵ and R⁶ above), cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)₂ (and these alkyl groups may join to form a ring as described for R⁵ and R⁶ above), CO₂H, CO₂(C₁₋₄ alkyl), NHC(O)(C₁₋₄ alkyl), NHS(O)₂(C₁₋₄ alkyl), C(O)(C₁₋₄ alkyl), CF₃ or OCF₃);

alkyl), $S(O)_2N(C_{1-4} \text{ alkyl})_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4} \text{ alkyl})$, $C(O)N(C_{1-4} \text{ alkyl})_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), CO_2H , $CO_2(C_{1-4} \text{ alkyl})$, $NHC(O)(C_{1-4} \text{ alkyl})$, $NHS(O)_2(C_{1-4} \text{ alkyl})$, $C(O)(C_{1-4} \text{ alkyl})$, CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2 , $NH(C_{1-4} \text{ alkyl})$, $N(C_{1-4} \text{ alkyl})_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), $S(O)_2(C_{1-4} \text{ alkyl})$, $S(O)_2NH_2$, $S(O)_2NH(C_{1-4} \text{ alkyl})$, $S(O)_2N(C_{1-4} \text{ alkyl})_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4} \text{ alkyl})$, $C(O)N(C_{1-4} \text{ alkyl})_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), CO_2H , $CO_2(C_{1-4} \text{ alkyl})$, $NHC(O)(C_{1-4} \text{ alkyl})$, $NHS(O)_2(C_{1-4} \text{ alkyl})$, $C(O)(C_{1-4} \text{ alkyl})$, CF_3 or OCF_3);

R^{24} is hydrogen, C_{1-6} alkyl or benzyl;

or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate thereof.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate. Another example of an addition salt is sulphate. Salts also include metal salts, such as a sodium, potassium, magnesium or calcium salt.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Halogen includes fluorine, chlorine, bromine and iodine. Halogen is, for example, fluorine or chlorine.

Alkyl groups and moieties are straight or branched chain and are, for example, methyl, ethyl, *n*-propyl, *iso*-propyl or *tert*-butyl.

Alkenyl groups are, for example, vinyl or allyl.

Cycloalkyl is mono-, bi or tricyclic and is, for example, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl or camphoryl. The cycloalkyl ring is optionally fused to a benzene ring (for example forming a bicyclo[4.2.0]octa-1,3,5-trienyl or indanyl ring system).

Cycloalkenyl is, for example, monocyclic and is, for example, cyclopentenyl or cyclohexenyl.

Aryl is, for example, phenyl or naphthyl.

Heterocyclyl is an aromatic or non-aromatic 5 or 6 membered ring, optionally fused
 5 to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heterocyclyl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, pyridinyl (for example in 6-oxo-1,6-dihydro-pyridinyl),
 10 pyrimidinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl (also known as benzofuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), 2,3-dihydrobenz[b]thienyl (for example in 1-dioxo-2,3-dihydrobenz[b]thienyl), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl (for example in 1H-benzthiazol-2-one-yl), 2,3-dihydrobenzthiazolyl (for example in 2,3-dihydrobenzthiazol-2-one-yl), 1,2,3-
 15 benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2a]pyridinyl), thieno[3,2-b]pyridin-6-yl 1,2,3-benzoxadiazolyl, benzo[1,2,3]thiadiazolyl, 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, dihydro-1-benzopyryliumyl (for example in a coumarinyl or a chromonyl), 3,4-dihydro-1H-2,1-benzothiazinyl (for example in 2-dioxo-3,4-dihydro-1H-2,1-benzothiazinyl), a
 20 pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), a purine (for example in 3,7-dihydro-purin-2,6-dione-8-yl), quinolinyl, isoquinolinyl (for example in 2H-isoquinolin-1-one-yl), a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl or in 1H-[1,8]naphthyridin-4-one-yl), a benzothiazinyl (for example in 4H-benzo[1,4]thiazin-3-one-yl), benzo[d]imidazo[2,1-b]thiazol-2-yl or dibenzothiophenyl (also known as
 25 dibenzothiienyl); or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heterocyclyl also includes isothiazolyl.

An N-oxide of a compound of formula (I) is, for example, a 1-oxy-[1,4']bipiperidinyl-1'-yl compound.

In one particular aspect the invention provides a compound of formula (I) wherein
 30 X is O.

In a further aspect R²⁴ is hydrogen.

In another aspect R¹ is phenyl optionally substituted with fluorine, chlorine, C₁₋₄ alkyl (for example methyl) or C₁₋₄ alkoxy (for example methoxy).

In yet another aspect R^1 is phenyl optionally substituted (for example with one, two or three) with fluorine, chlorine, C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy). In a further aspect R^1 is phenyl optionally substituted (for example with one, two or three) with fluorine, chlorine or C_{1-4} alkyl (for example methyl). In a still further aspect R^1 is phenyl substituted by one, two or three of fluorine, chlorine, methyl or methoxy. For example R^1 is 3,4-dichlorophenyl, 2,4-dichloro-3-methylphenyl, 3,4-dichloro-2-methylphenyl, 2,4-dichlorophenyl, 4-chloro-2-methylphenyl or 2-chloro-4-fluorophenyl.

In a still further aspect R^1 is phenyl optionally substituted (for example independently di-substituted) with halogen (for example chlorine) or C_{1-4} alkyl (for example methyl).

In a further aspect R^2 is unsubstituted phenyl, mono-substituted phenyl or mono-substituted heterocyclyl, the substituents being chosen from those described above.

In a still further aspect R^2 is oxo substituted heterocyclyl, said heterocyclyl optionally further substituted with one or more substituents chosen from those described above.

In another aspect R^2 is phenyl or heterocyclyl, either of which is optionally substituted by: halo, hydroxy, nitro, cyano, amino, C_{1-4} alkyl (itself optionally substituted by $S(O)_2(C_{1-4} \text{ alkyl})$ or $S(O)_2\text{phenyl}$), C_{1-4} alkoxy, $S(O)_pR^4$ (wherein p is 0, 1 or 2 (for example 2)), $C(O)NH_2$, $NHS(O)_2(C_{1-4} \text{ alkyl})$, $S(O)_2NH_2$, $S(O)_2NH(C_{1-4} \text{ alkyl})$ or $S(O)_2N(C_{1-4} \text{ alkyl})_2$; and R^4 is C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl(C_{1-4} alkyl) (such as cyclopropylmethyl).

In a further aspect R^2 is phenyl mono-substituted by halo, hydroxy, nitro, cyano, amino, C_{1-4} alkyl (itself optionally substituted by $S(O)_2(C_{1-4} \text{ alkyl})$ or $S(O)_2\text{phenyl}$), C_{1-4} alkoxy, $S(O)_pR^4$ (wherein p is 0, 1 or 2 (for example 2)), $C(O)NH_2$, $NHS(O)_2(C_{1-4} \text{ alkyl})$, $S(O)_2NH_2$, $S(O)_2NH(C_{1-4} \text{ alkyl})$ or $S(O)_2N(C_{1-4} \text{ alkyl})_2$; and R^4 is C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl(C_{1-4} alkyl) (such as cyclopropylmethyl).

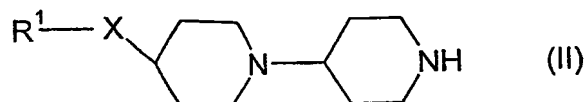
In yet another aspect R^2 is phenyl (optionally substituted by C_{1-6} alkyl (itself optionally mono-substituted by hydroxy), C_{1-6} alkoxy or phenyl), naphthylenyl (optionally substituted by C_{1-4} alkoxy) or heterocyclyl.

Heterocyclyl is, for example, thienyl, furanyl, benzofuranyl or benzo[b]thienyl. In a further aspect of the invention heterocyclyl is optionally substituted by halogen, C_{1-4} alkyl or C_{1-4} alkoxy.

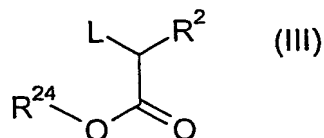
In a further aspect the present invention provides a compound of formula (I) wherein X is O; R¹ is phenyl optionally substituted by halogen (for example chlorine) or C₁₋₄ alkyl (for example methyl); and R² is as defined above.

A compound of formula (I) can be prepared by coupling a compound of formula

5 (II):

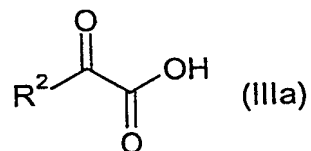


with a compound of formula (III):



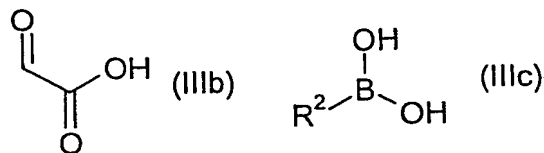
10 wherein L is a suitable leaving group (such as can be halogen (such as chloro) or C₁₋₆ alkylsulfonyl) and the coupling can be carried out in a suitable solvent (such as water).

Alternatively, a compound of formula (I) can be prepared by reductive amination of a compound (II) with an ester (such as a C₁₋₆ alkyl ester or a benzyl ester) of a compound of formula (IIIa):



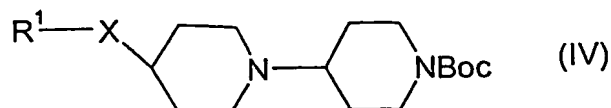
15 in the presence of NaBH(OAc)₃ and acetic acid, optionally followed by removal of the ester group.

Alternatively, a compound of formula (I) where R²⁴ represents H can be prepared by a three component coupling of a compound of formula (II) with compounds of formula (IIIb) and (IIIc):



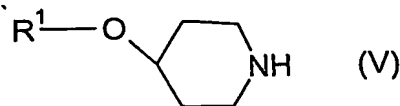
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A compound of formula (II) can be prepared by deprotecting a compound of formula (IV):

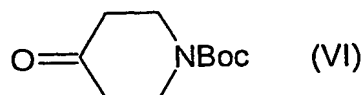


for example using trifluoroacetic acid in a suitable solvent (such as dichloromethane) or using a source of hydrogen chloride in a suitable solvent (such as dioxane).

A compound of formula (IV), wherein X is O, can be prepared by reacting a
5 compound of formula (V):

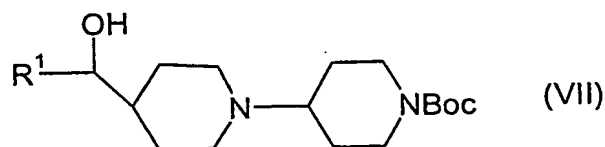


with a compound of formula (VI):

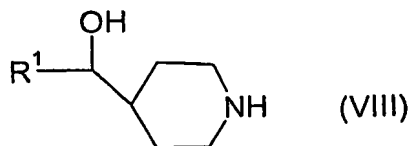


in the presence of $\text{NaBH}(\text{OAc})_3$ and acetic acid.

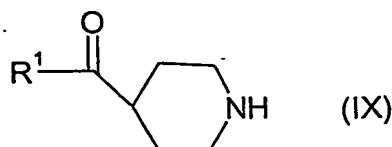
10 A compound of formula (IV), wherein X is CO or CH_2 , can be prepared by oxidising or reducing a compound of formula (VII):



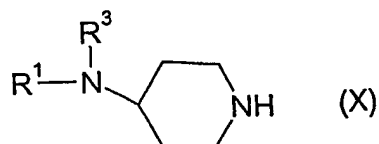
A compound of formula (VII) can be prepared by reacting a compound of formula (VIII):



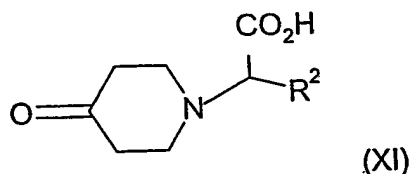
15 with a compound of formula (VI) in the presence of $\text{NaBH}(\text{OAc})_3$ and acetic acid. A compound of formula (VIII) can be prepared by reduction of a compound of formula (IX):



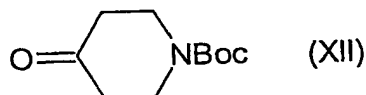
A compound of formula (I) wherein X is NR^3 can be prepared by reacting a compound of formula (X):



with a compound of formula (XI):

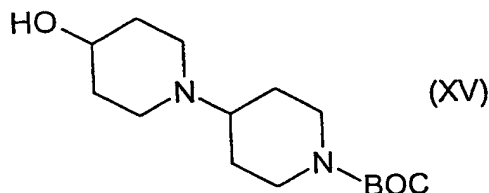


in the presence of NaBH(OAc)₃ and acetic acid. A compound of formula (X) can be prepared by reacting NHR¹R³ with a compound of formula (XII):

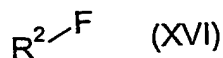


in the presence of NaBH(OAc)₃ and acetic acid and then deprotecting the piperidine nitrogen {for example using trifluoroacetic acid in a suitable solvent (such as dichloromethane) or using a source of hydrogen chloride in a suitable solvent (such as dioxane)}.

Compounds (IV) where X is O and R¹ represents aryl or heterocyclyl may be prepared from a compound of formula (XV):



and a compound of formula (XVI):



for example using potassium t-butoxide in N-methylpyrrolidinone, for example at 60°.

Compounds of formula (I) where R²⁴ is hydrogen may be converted to compounds of formula (I) where R²⁴ is not hydrogen by standard esterification methods well known in the art.

Compounds of formula (I) where R²⁴ is not hydrogen may be converted to compounds of formula (I) where R²⁴ is hydrogen by standard ester hydrolysis methods well known in the art.

The preparation of various intermediates can be found in WO00/66559 and WO01/77101; alternatively they can be prepared by using or adapting literature methods.

Further compounds of formula (I) can be prepared by adaptation of: the routes described above, methods described in the art or the Examples recited below.

5 Compounds of formula (V), (VI), (IX), (XI), (XII), (XV) and (XVI) can be prepared by using or adapting methods described in the art.

In another aspect the present invention provides processes for the preparation of compounds of formula (I).

10 The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (for example CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

Examples of these conditions are:

- 15 (1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including
- 20 rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive
- 25 activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;
- (2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;
- 30 (3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatides, seborrhoetic dermatitis, lichen planus, pemphigus, bullous pemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata, corneal ulcer or vernal conjunctivitis;

- (4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);
- 5 (5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or
- 10 (6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), periodontal disease, Sezary syndrome, idiopathic thrombocytopenia purpura or disorders of the menstrual cycle.

The compounds of formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof, are also H1 antagonists (and can, therefore, be used in the treatment of allergic disorders); and may also be used to control a sign and/or symptom of what is commonly referred to as a cold (for example a sign and/or symptom of a common cold or influenza or other associated respiratory virus infection).

According to a further feature of the present invention there is provided a method for treating a chemokine mediated disease state (for example a CCR3 mediated disease state) in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof.

25 According to another feature of the present invention there is provided a method for antagonising H1 in a mammal, such as man, suffering from, or at risk of, an H1 mediated disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof.

30 According to yet another feature of the present invention there is provided a method for treating a sign and/or symptom of what is commonly referred to as a cold in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of

a compound of the formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof.

The invention also provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in therapy.

5 In another aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (for example CCR3 receptor activity), antagonising H1 or treating a sign and/or symptom of what is commonly referred to as a cold).

10 The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

- (1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, 15 allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or 20 pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;
- 25 (2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis;
- (3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermitides, seborrhoetic dermatitis, lichen planus, phemphigus, bullous phemphigus, 30 epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata, corneal ulcer or vernal conjunctivitis;
- (4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-

related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

- (5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or
- (6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;
- in a mammal (for example man).

In a further aspect the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)); or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a still further aspect a compound of formula (I), or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma.

The present invention also provides a the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)); or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a mammal, such as man, said

ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier.

In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will, for example, comprise from 0.05 to 99 %w (per cent by weight), such as from 0.05 to 80 %w, for example from 0.10 to 70 %w, such as from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art. A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

Each patient may receive, for example, a dose of 0.01mgkg^{-1} to 100mgkg^{-1} , for example in the range of 0.1mgkg^{-1} to 20mgkg^{-1} , of the active ingredient administered, for example, 1 to 4 times per day.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

- (i) when given, ^1H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300MHz or 400MHz using perdeuterio DMSO-D₆ (CD_3SOCD_3) or CDCl_3 as the solvent unless otherwise stated;
- (ii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(\text{M}+\text{H})^+$;
- (iii) the title and sub-title compounds of the examples and methods were named using the

index name program from Advanced Chemistry Development Inc;

(iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry™,

NovaPak™ or Xerra™ reverse phase silica column; and

(v) the following abbreviations are used:

| | |
|------------|-------------------------------------|
| Boc or BOC | <u>tert</u> -butoxycarbonyl |
| HPLC | high pressure liquid chromatography |

| | |
|------|-------------------|
| DMSO | dimethylsulfoxide |
| aq | aqueous |

EXAMPLE 1

This Example illustrates the preparation of 4-(3,4-dichlorophenoxy)- α -phenyl-[1,4'-bipiperidine]-1'-acetic acid.

To a solution of 4-(3,4-dichlorophenoxy)-1,4'-bipiperidine (WO 01/77101) (0.500g) in water (5 ml) was added bromo(phenyl)acetic acid (0.348g) and the reaction was left to stir for 16hrs. Evaporation of solvent and purification using reverse phase HPLC (with a gradient eluent system of 5% MeCN/ NH₄OAc_(aq) (0.1%) to 95% MeCN/NH₄OAc_(aq) (0.1%) gave the title compound as a solid (0.049g).

MS: APCI(-ve): 461 (M-H)⁻

¹H NMR (CDCl₃) δ 1.80 - 2.05 (6H, m), 2.33 - 2.78 (5H, m), 3.25 - 3.56 (7H, m), 4.23 - 4.26 (2H, m), 6.69 (1H, dd), 6.93 (1H, d), 7.28 - 7.36 (4H, m), 7.52 - 7.55 (2H, m).

EXAMPLE 2

This Example illustrates the preparation of 4-(3,4-dichlorophenoxy)- α -(2,6-dimethoxyphenyl)-[1,4'-bipiperidine]-1'-acetic acid.

To a solution of 4-(3,4-dichlorophenoxy)-1,4'-bipiperidine (0.500g) in ethanol (3ml) was added 2,6-dimethoxyphenylboronic acid (0.275g) and oxoacetic acid (0.1ml). The mixture was heated to 80°C for 5 minutes using microwaves at 50 Watts. The solvent was removed by evaporation. Purification using reverse phase HPLC (with a gradient eluent system of 5% MeCN/NH₃(aq) (0.2%) to 95% MeCN/NH₃(aq) (0.2%) gave the title compound (0.210g).

MS: ES(+ve): 523 (M+H)⁺

¹H NMR (CDCl₃) δ 1.75 - 1.77 (2H, m), 1.89 - 1.97 (5H, m), 2.04 - 2.10 (1H, m), 2.39 - 2.43 (4H, m), 2.73 - 2.75 (2H, m), 2.84 - 2.90 (1H, m), 3.48 - 3.53 (2H, m), 3.84

(6H, s), 4.20 - 4.26 (1H, m), 5.00 (1H, s), 6.59 - 6.61 (2H, m), 6.71 - 6.74 (1H, m), 6.96 - 6.97 (1H, m), 7.27 - 7.34 (2H, m).

EXAMPLE 3

5 This Example illustrates the preparation of 4-(4-chloro-2-methylphenoxy)- α -phenyl-[1,4'-bipiperidine]-1'-acetic acid.

To a solution of 4-(4-chloro-2-methylphenoxy)-1,4'-bipiperidine (0.540g) (WO 01/77101) in acetonitrile (5ml) was added phenylboronic acid (0.212g) and oxoacetic acid (0.1ml). The mixture was heated to 100°C for 4 minutes using microwaves at 50 Watts.
10 The crude reaction was put onto an Oasis® MCX cartridge (Waters Chromatography) in MeOH and the cartridge washed with MeOH followed by elution with 20%/NH_{3(aq)}/MeOH. Evaporation of solvent and further purification by reverse phase HPLC (with a gradient eluent system of 5% MeCN/NH_{3(aq)} (0.2%) to 95% MeCN/NH_{3(aq)} (0.2%) gave the title compound (0.052g).

15 MS: APCI(+ve): 443 (M+H)⁺

¹H NMR (CD₃OD) δ 1.84 - 2.11 (8H, m), 2.18 (3H, s), 2.69 - 3.01 (8H, m), 3.72 (1H, s), 4.27 (1H, s), 4.42 - 4.47 (1H, m), 6.88 (1H, d), 7.07 - 7.12 (2H, m), 7.39 - 7.43 (3H, m), 7.54 - 7.57 (2H, m).

20 EXAMPLE 4

This Example illustrates the preparation of methyl 4-(3,4-dichlorophenoxy)- α -phenyl-[1,4'-bipiperidine]-1'-acetate

4-(3,4-Dichlorophenoxy)-1,4'-bipiperidine (0.20g) and methyl- α -bromophenylacetate (0.14g) were dissolved in acetone (20mL). Potassium carbonate
25 (0.08g) was added. The reaction mixture was stirred at room temperature for 16 h, then filtered and purified via RPHPLC (gradient Ammonium acetate/Acetonitrile 75% to 5% aqueous; Symmetry column) to give the title compound (0.09g).

MS [M+H]⁺ (ES+) 477

¹H NMR δ (CD₃OD) 1.46 - 1.53 (1H, m), 1.56 - 1.63 (1H, m), 1.66 - 1.76 (2H, m),
30 1.77 - 1.86 (3H, m), 1.89 - 1.98 (2H, m), 2.04 - 2.13 (1H, m), 2.29 - 2.40 (1H, m), 2.48 - 2.57 (2H, m), 2.64 - 2.71 (1H, m), 2.78 - 2.88 (2H, m), 2.94 - 3.01 (1H, m), 3.56 (3H, s), 3.93 (1H, s), 4.30 - 4.37 (1H, m), 6.79 (1H, dd), 7.01 (1H, d), 7.22 - 7.34 (6H, m).

EXAMPLES 5-24

Examples 5-24 are examples of compounds of formula (I) and were prepared by the following general method.

To a solution of 4-(3,4-dichlorophenoxy)-1,4'-bipiperidine (0.004 g) in dimethyl acetamide (0.150ml) was added appropriate boronic acid (1 molar equivalent in 0.2ml of dimethylacetamide) and oxoacetic acid (1.5 molar equivalents). The mixture was heated to 80°C for 5 minutes using microwaves at 300 Watts. Purification using reverse phase HPLC [with a gradient eluent system of 5% MeCN/NH_{3(aq)} (0.2%) to 95% MeCN/NH_{3(aq)} (0.2%)] gave the required product.

| Example | Name | (M+H) ⁺ |
|---------|---|--------------------|
| 5 | 4-(3,4-dichlorophenoxy)-α-[3-(hydroxymethyl)phenyl]-[1,4'-bipiperidine]-1'-acetic acid | 493 |
| 6 | 4-(3,4-dichlorophenoxy)-α-(6-methoxy-2-naphthalenyl)-[1,4'-bipiperidine]-1'-acetic acid | 543 |
| 7 | 4-(3,4-dichlorophenoxy)-α-phenyl-[1,4'-bipiperidine]-1'-acetic acid | 463 |
| 8 | 4-(3,4-dichlorophenoxy)-α-(4-methylphenyl)-[1,4'-bipiperidine]-1'-acetic acid | 477 |
| 9 | 4-(3,4-dichlorophenoxy)-α-(2-thienyl)-[1,4'-bipiperidine]-1'-acetic acid | 469 |
| 10 | 4-(3,4-dichlorophenoxy)-α-(3-thienyl)-[1,4'-bipiperidine]-1'-acetic acid | 469 |
| 11 | α-(2-benzofuranyl)-4-(3,4-dichlorophenoxy)-[1,4'-bipiperidine]-1'-acetic acid | 503 |
| 12 | 4-(3,4-dichlorophenoxy)-α-[4-(1,1-dimethylethoxy)phenyl]-[1,4'-bipiperidine]-1'-acetic acid | 536 |
| 13 | 4-(3,4-dichlorophenoxy)-α-(3-methylphenyl)-[1,4'-bipiperidine]-1'-acetic acid | 477 |
| 14 | 4-(3,4-dichlorophenoxy)-α-(1-naphthalenyl)-[1,4'-bipiperidine]-1'-acetic acid | 513 |

| | | |
|----|---|-----|
| 15 | 4-(3,4-dichlorophenoxy)- α -(2-naphthalenyl)-[1,4'-bipiperidine]-1'-acetic acid | 513 |
| 16 | α -benzo[b]thien-2-yl-4-(3,4-dichlorophenoxy)-[1,4'-bipiperidine]-1'-acetic acid | 519 |
| 17 | α -[1,1'-biphenyl]-3-yl-4-(3,4-dichlorophenoxy)-[1,4'-bipiperidine]-1'-acetic acid | 540 |
| 18 | 4-(3,4-dichlorophenoxy)- α -(2,6-dimethoxyphenyl)-[1,4'-bipiperidine]-1'-acetic acid | 523 |
| 19 | 4-(3,4-dichlorophenoxy)- α -(3,4-dimethoxyphenyl)-[1,4'-bipiperidine]-1'-acetic acid | 523 |
| 20 | 4-(3,4-dichlorophenoxy)- α -(2,4-dimethoxyphenyl)-[1,4'-bipiperidine]-1'-acetic acid | 523 |
| 21 | 4-(3,4-dichlorophenoxy)- α -[3-(1-methylethyl)phenyl]-[1,4'-bipiperidine]-1'-acetic acid | 505 |
| 22 | 4-(3,4-dichlorophenoxy)- α -(3,4,5-trimethoxyphenyl)-[1,4'-bipiperidine]-1'-acetic acid | 553 |
| 23 | 4-(3,4-dichlorophenoxy)- α -[4-(1,1-dimethylethyl)phenyl]-[1,4'-bipiperidine]-1'-acetic acid | 520 |

EXAMPLE 24

Pharmacological Analysis: Calcium flux [Ca^{2+}]_i assay

5 Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended ($5 \times 10^6 \text{ ml}^{-1}$) and loaded with $5 \mu\text{M}$ FLUO-3/AM + Pluronic F127 $2.2 \mu\text{l/ml}$ (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, MgSO_4 0.8mM, glucose 5.5mM, Na_2CO_3 8.5mM, KCl 5mM, HEPES 20mM, CaCl_2 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5 \times 10^6 \text{ ml}^{-1}$. The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with

5µM fibronectin for two hours) at 25µl/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200µl; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A₅₀ concentration of eotaxin and the transient increase in fluo-3 fluorescence (I_{Ex} = 490nm and I_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

EXAMPLE 25

Human eosinophil chemotaxis

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at 10x10⁶ ml⁻¹ in RPMI containing 200 IU/ml penicillin, 200 µg/ml streptomycin sulphate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700 µl) were pre-incubated for 15 mins at 37° C with 7 µl of either vehicle or compound (100x required final concentration in 10% DMSO). The chemotaxis plate (ChemoTx, 3µm pore, Neuroprobe) was loaded by adding 28µl of a concentration of eotaxin (0.1 to 100nM) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 µl of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO₂ atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 µl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Compounds of the Examples were found to be antagonists of the eotaxin mediated human eosinophil chemotaxis.

| Example | % Inhibition (3 nM Human Eotaxin) |
|---------|-----------------------------------|
| 2 | 90 |
| 3 | 105 |

EXAMPLE 26

5 Guinea-pig isolated trachea

(See for example, Harrison, R.W.S., Carswell, H. & Young, J.M. (1984) European J. Pharmacol., 106, 405-409.)

Male albino Dunkin-Hartley guinea-pigs (250g) were killed by cervical dislocation and the whole trachea removed. After clearing the adherent connective tissue, the trachea was cut
10 into six ring segments each three cartilage bands wide and then suspended in 20ml organ baths containing Krebs-Henseleit solution of the following composition (mM): NaCl 117.6, NaH_2PO_4 0.9, NaHCO_3 25.0, MgSO_4 1.2, KCl 5.4, CaCl_2 2.6 and glucose 11.1. The buffer was maintained at 37°C and gassed with 5% CO_2 in oxygen. Indomethacin (2.8 μM) was added to the Krebs solution to prevent development of smooth muscle tone due to the synthesis of cyclo-
15 oxygenase products. The tracheal rings were suspended between two parallel tungsten wire hooks, one attached to an Ormed beam isometric force transducer and the other to a stationary support in the organ bath. Changes in isometric force were recorded on 2-channel Sekonic flat bed chart recorders.

Experimental protocols

20 At the beginning of each experiment a force of 1g was applied to the tissues and this was reinstated over a 60 minute equilibration period until a steady resting tone was achieved. Subsequently, a cumulative histamine concentration effect ($\text{E}/[\text{A}]$) curve was constructed at 0.5 \log_{10} unit increments, in each tissue. The tissues were then washed and approximately 30 minutes later, test compound or vehicle (20% DMSO) was added. Following an incubation
25 period of 60 minutes a second $\text{E}/[\text{A}]$ curve was performed to histamine.

Contraction responses were recorded as a percentage of the first curve maximum.

Data analysis

Experimental $\text{E}/[\text{A}]$ curve data were analysed for the purposes of estimating the potencies ($\text{p}[\text{A}_{50}]$ values) of histamine in the absence and presence of the test compound.

Affinity (pA_2) values of test compounds were subsequently calculated using the following equation:

$$\log(r-1) = \log[B] + pA_2$$

where $r = [A]_{50}$ in presence of test compound/ $[A]_{50}$ in absence of antagonist and $[B]$ is the concentration of test compound. Compounds of the Examples were found to be H1 antagonists.

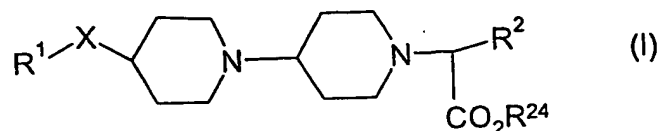
EXAMPLE 27

Histamine H1 receptor binding activity of compounds of the invention was assessed by competition displacement of 1nM $[3H]$ -pyrilamine (Amersham, Bucks, Product code TRK 608, specific activity 30Ci/mmol) to 2 μ g membranes prepared from recombinant CHO-K1 cells expressing the human H1 receptor (Euroscreen SA, Brussels, Belgium, product code ES-390-M) in assay buffer (50mM Tris pH 7.4 containing 2mM $MgCl_2$, 250mM sucrose and 100mM NaCl) for 1 hour at room temperature. The following compounds of the invention gave inhibition of $[3H]$ pyrilamine binding:

| Example | H1 antagonism pK_i |
|---------|----------------------|
| 1 | 7.2 |
| 2 | 6.8 |
| 3 | 7.3 |
| 4 | 7.2 |

CLAIMS

1. A compound of formula (I):



wherein:

X is CH₂, C(O), O, S, S(O), S(O)₂ or NR³;

R¹ is hydrogen, C₁₋₆ alkyl, aryl or heterocyclyl;

R² is C₃₋₇ cycloalkyl {optionally substituted by C₁₋₄ alkyl, aryl or oxo}, C₃₋₇

cycloalkenyl {optionally substituted by oxo, C₁₋₆ alkyl or aryl}, aryl or

heterocyclyl;

wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by:

halogen, cyano, nitro, hydroxy, oxo, S(O)_pR⁴, OC(O)NR⁵R⁶, NR⁷R⁸, NR⁹C(O)R¹⁰,
NR¹¹C(O)NR¹²R¹³, S(O)₂NR¹⁴R¹⁵, NR¹⁶S(O)₂R¹⁷, C(O)NR¹⁸R¹⁹, C(O)R²⁰, CO₂R²¹,

NR²²CO₂R²³, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆

haloalkoxy, C₁₋₆ alkoxy(C₁₋₆)alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkylthio, C₂₋₆ alkenyl,

C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl (itself optionally substituted by C₁₋₄ alkyl or oxo),

methylenedioxy, difluoromethylenedioxy, phenyl, phenyl(C₁₋₄)alkyl, phenoxy,

phenylthio, phenyl(C₁₋₄)alkoxy, heterocyclyl, heterocyclyl(C₁₋₄)alkyl,

heterocycliloxy or heterocyclyl(C₁₋₄)alkoxy; wherein any of the immediately

foregoing phenyl and heterocyclyl moieties are optionally substituted with halogen,

hydroxy, nitro, S(O)_q(C₁₋₄ alkyl), S(O)₂NH₂, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy,

C(O)NH₂, C(O)NH(C₁₋₄ alkyl), C(O)N(C₁₋₄ alkyl)₂ (and these alkyl groups may join

to form a ring as described for R⁵ and R⁶ below), CO₂H, CO₂(C₁₋₄ alkyl),

NHC(O)(C₁₋₄ alkyl), NHS(O)₂(C₁₋₄ alkyl), C(O)(C₁₋₄ alkyl), CF₃ or OCF₃;

p and q are, independently, 0, 1 or 2;

R³, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁸, R¹⁹, R²⁰, R²¹ and R²² are,

independently, hydrogen, C₁₋₆ alkyl (optionally substituted by halogen, hydroxy or

C₃₋₁₀ cycloalkyl), CH₂(C₂₋₆ alkenyl), phenyl (itself optionally substituted by

halogen, hydroxy, nitro, NH₂, NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)₂, S(O)₂(C₁₋₄ alkyl),

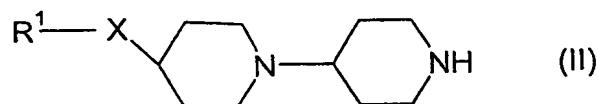
S(O)₂NH₂, cyano, C₁₋₄ alkyl, C₁₋₄ alkoxy, C(O)NH₂, C(O)NH(C₁₋₄ alkyl),

C(O)N(C₁₋₄ alkyl)₂ (and these alkyl groups may join to form a ring as described for

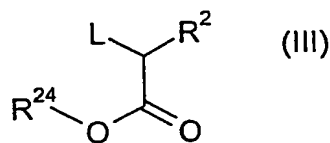
R^5 and R^6 below), CO_2H , $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$, $\text{NHC}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, $\text{NHS}(\text{O})_2(\text{C}_{1-4} \text{ alkyl})$, $\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, CF_3 or OCF_3) or heterocyclcyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2 , $\text{NH}(\text{C}_{1-4} \text{ alkyl})$, $\text{N}(\text{C}_{1-4} \text{ alkyl})_2$, $\text{S}(\text{O})_2(\text{C}_{1-4} \text{ alkyl})$, $\text{S}(\text{O})_2\text{NH}_2$, $\text{S}(\text{O})_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$, $\text{S}(\text{O})_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$ (and these alkyl groups may
5 join to form a ring as described for R^5 and R^6 below), cyano, $\text{C}_{1-4} \text{ alkyl}$, $\text{C}_{1-4} \text{ alkoxy}$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NH}(\text{C}_{1-4} \text{ alkyl})$, $\text{C}(\text{O})\text{N}(\text{C}_{1-4} \text{ alkyl})_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 below), CO_2H , $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$, $\text{NHC}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, $\text{NHS}(\text{O})_2(\text{C}_{1-4} \text{ alkyl})$, $\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, CF_3 or OCF_3); alternatively NR^5R^6 , NR^7R^8 , $\text{NR}^{12}\text{R}^{13}$, $\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{18}\text{R}^{19}$, may, independently,
10 form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, 1,4-morpholine or 1,4-piperazine, the latter optionally substituted by $\text{C}_{1-4}\text{alkyl}$ on the distal nitrogen;
 R^4 , R^{17} and R^{23} are, independently, $\text{C}_{1-6} \text{ alkyl}$ (optionally substituted by halogen, hydroxy or $\text{C}_{3-10} \text{ cycloalkyl}$), $\text{CH}_2(\text{C}_{2-6} \text{ alkenyl})$, phenyl (itself optionally substituted
15 by halogen, hydroxy, nitro, NH_2 , $\text{NH}(\text{C}_{1-4} \text{ alkyl})$, $\text{N}(\text{C}_{1-4} \text{ alkyl})_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), $\text{S}(\text{O})_2(\text{C}_{1-4} \text{ alkyl})$, $\text{S}(\text{O})_2\text{NH}_2$, $\text{S}(\text{O})_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$, $\text{S}(\text{O})_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), cyano, $\text{C}_{1-4} \text{ alkyl}$, $\text{C}_{1-4} \text{ alkoxy}$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NH}(\text{C}_{1-4} \text{ alkyl})$, $\text{C}(\text{O})\text{N}(\text{C}_{1-4} \text{ alkyl})_2$ (and these alkyl groups may
20 join to form a ring as described for R^5 and R^6 above), CO_2H , $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$, $\text{NHC}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, $\text{NHS}(\text{O})_2(\text{C}_{1-4} \text{ alkyl})$, $\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, CF_3 or OCF_3) or heterocyclcyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2 , $\text{NH}(\text{C}_{1-4} \text{ alkyl})$, $\text{N}(\text{C}_{1-4} \text{ alkyl})_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), $\text{S}(\text{O})_2(\text{C}_{1-4} \text{ alkyl})$, $\text{S}(\text{O})_2\text{NH}_2$, $\text{S}(\text{O})_2\text{NH}(\text{C}_{1-4} \text{ alkyl})$,
25 $\text{S}(\text{O})_2\text{N}(\text{C}_{1-4} \text{ alkyl})_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), cyano, $\text{C}_{1-4} \text{ alkyl}$, $\text{C}_{1-4} \text{ alkoxy}$, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NH}(\text{C}_{1-4} \text{ alkyl})$, $\text{C}(\text{O})\text{N}(\text{C}_{1-4} \text{ alkyl})_2$ (and these alkyl groups may join to form a ring as described for R^5 and R^6 above), CO_2H , $\text{CO}_2(\text{C}_{1-4} \text{ alkyl})$, $\text{NHC}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, $\text{NHS}(\text{O})_2(\text{C}_{1-4} \text{ alkyl})$, $\text{C}(\text{O})(\text{C}_{1-4} \text{ alkyl})$, CF_3 or OCF_3);
30 R^{24} is hydrogen, $\text{C}_{1-6} \text{ alkyl}$ or benzyl;
or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate thereof.

2. A compound of formula (I) as claimed in claim 1 wherein X is O.
3. A compound of formula (I) as claimed in claim 1 or 2 wherein R²⁴ is hydrogen.
- 5 4. A compound of formula (I) as claimed in claim 1, 2 or 3 wherein R¹ is phenyl optionally substituted with fluorine, chlorine, C₁₋₄ alkyl or C₁₋₄ alkoxy.
- 10 5. A compound of formula (I) as claimed in claim 1, 2, 3 or 4 wherein R² is phenyl or heterocyclyl, either of which is optionally substituted by: halo, hydroxy, nitro, cyano, amino, C₁₋₄ alkyl (itself optionally substituted by S(O)₂(C₁₋₄ alkyl) or S(O)₂phenyl), C₁₋₄ alkoxy, S(O)_pR⁴ (wherein p is 0, 1 or 2), C(O)NH₂, NHS(O)₂(C₁₋₄ alkyl), S(O)₂NH₂, S(O)₂NH(C₁₋₄ alkyl) or S(O)₂N(C₁₋₄ alkyl)₂; and R⁴ is C₁₋₄ alkyl, C₁₋₄ hydroxyalkyl, C₃₋₇ cycloalkyl or C₃₋₇ cycloalkyl(C₁₋₄ alkyl).
- 15 6. A process for preparing a compound of formula (I) as claimed in claim 1, the process comprising:

- i. coupling a compound of formula (II):

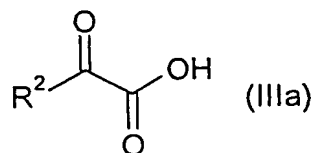


with a compound of formula (III):



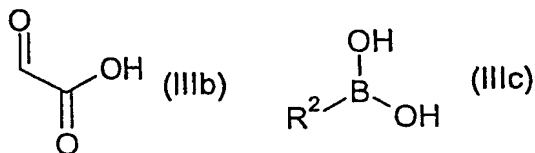
wherein L is a suitable leaving group, in a suitable solvent; or,

- ii. reductive amination of a compound (II) with an ester compound of formula (IIIa):



in the presence of NaBH(OAc)₃ and acetic acid, followed optionally by removal of the ester group; or

- iii. a three component coupling of a compound of formula (II) with compounds of formula (IIIb) and (IIIc):



- 5 7. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, and a pharmaceutically acceptable adjuvant, diluent or carrier.
- 10 8. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, for use in therapy.
- 15 9. A compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, in the manufacture of a medicament for use in therapy.
- 20 10. A method of treating a chemokine mediated disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/00442

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/04, C07D 409/14, C07D 405/14, A61K 31/445, A61P 37/00, A61P 11/06, A61P 31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| X | WO 0177101 A1 (ASTRAZENECA AB), 18 October 2001 (18.10.01) -- | 1-10 |
| X | WO 0066559 A1 (SCHERING CORPORATION), 9 November 2000 (09.11.00) -- | 1-10 |
| A | WO 0129066 A2 (MENARINI RICERCHE S.P.A.), 26 April 2001 (26.04.01), RN 34942-07-3 page 5, line 15 - line 19, page 22, line 23 - line 28 -- | 1-10 |
| A | WO 9641631 A1 (ELI LILLY AND COMPANY), 27 December 1996 (27.12.96), page 16, line 19 - page 17, line 21 -- | 1-10 |

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 May 2003

Date of mailing of the international search report

06-06-2003

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/00442

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | WO 9310091 A2 (GLAXO GROUP LIMITED), 27 May 1993 (27.05.93), RN 150072-9-6, page 69, line 24 - line 25, page 54, line 14 - line 22 -- | 1-10 |
| A | STN International, File CAPLUS, CAPLUS accession no. 1988:630911, document no. 109:230911, Lehmann, Jochen et al: "Lactones. XVIII. Synthesis of lactone-bridged 1,1-diarylpropanamines"; & Arch. Pharm. (Weinheim, Ger.), 1988, 321(8), 443-5 ----- | 1-10 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/00442

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Claim 10 relates to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds or compositions. These alleged effects must be well defined diseases or conditions. The expression "a chemokine mediated disease state" may relate to a number of different disorders and conditions, which can not be clearly defined by this expression. Thus, the search has mainly been restricted to the diseases mentioned in the description on pages 10 to 13.

INTERNATIONAL SEARCH REPORT
Information on patent family members

29/04/03

International application No.

PCT/SE 03/00442

| Patent document cited in search report | | | | Publication date | | Patent family member(s) | Publication date |
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INTERNATIONAL SEARCH REPORT

Information on patent family members

29/04/03

International application No.

PCT/SE 03/00442

| Patent document cited in search report | | | Publication date | Patent family member(s) | Publication date |
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